**HUMAN FACTORS STUDY REPORT AND LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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| **Date of This Review:** | November 23, 2022 |
| **Requesting Center:** | Center for Biologics Research and Evaluation CBER/OTAT/DRPM/RPMB3 |
| **Application Type and Number:** | BLA 125771 |
| **Product Type:** | Combination Product (Biologic-Device) |
| **Biologic Constituent Name, Dosage Form and Strength:** | ALTUVIIIO [Antihemophilic Factor (Recombinant), Fc-Von Willebrand Factor-XTEN Fusion Protein] lyophilized powder for solution for intravenous injection, 250 units, 500 units, 750 units, 1,000 units, 2,000 units, 3,000 units, or 4,000 units |
| **Device Constituents:** | Prefilled diluent syringe, plunger rod, and vial adapter |
| **Rx or OTC:** | Prescription (Rx) |
| **Applicant Name:** | Bioverativ Therapeutics Inc. |
| **FDA Received Date:** | June 30, 2022 |
| **OSE RCM #:** | 2022-2130 |
| **DMEPA 2 Safety Evaluator:** | Millie Shah, PharmD, BCPS Millie Shah -S Digitally signed by Millie Shah -S Date: 2022.11.23 12:08:16 -05'00' |
| **DMEPA 2 Associate Director for Human Factors:** | Lolita White, PharmD Lolita G. White -S Digitally signed by Lolita G. White -S Date: 2022.11.23 21:28:59 -05'00' |
| **DMEPA 2 Division Director** | Danielle Harris, PharmD Danielle M. Harris -S Digitally signed by Danielle M. Harris -S Date: 2022.11.27 14:23:42 -05'00' |

## 1 REASON FOR REVIEW

This review responds to a CBER consult for DMEPA to evaluate the human factors (HF) validation study report and Instructions for Use (IFU) submitted under BLA 125771 for ALTUVIIIO ([Antihemophilic Factor (Recombinant), Fc-Von Willebrand Factor-XTEN Fusion Protein]) lyophilized powder for solution for intravenous injection. Specifically, CBER requested we:

1. assess whether the human factors engineering studies adequately evaluate user interactions with the product user interface
2. identify critical tasks that may result in serious harm to the patient or user
3. evaluate the effectiveness of risk control measures

### 1.1 PRODUCT INFORMATION

ALTUVIIIO, a biologic, is administered intravenously and is intended for use in adults and children with hemophilia A congenital factor VIII deficiency for:

- Routine prophylaxis to reduce the frequency of bleeding episodes,
- On demand treatment and control of bleeding episodes,
- Perioperative management of bleeding

This is a combination product with a proposed vial containing lyophilized efanesoctocog alfa powder and device constituent parts that include a prefilled syringe (PFS) containing 3 mL sterile water diluent, plunger rod, and vial adapter. An infusion set is needed to administer the product, and users will need to obtain the infusion set separately. The proposed product is intended for use by patients, lay caregivers, and healthcare professionals in the home or clinical setting.

See Appendix A for more information.

**Figure 1. ALTUVIIIO**


**Figure 2. ALTUVIIIO Packaging**

## 1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On August 30, 2021, the Applicant submitted an HF validation study protocol under IND 17464 for ALTUVIIIO and we provided recommendations for the Applicant.[a]

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

**Table 1. Materials Considered for this Label and Labeling Review**

| Material Reviewed | Appendix Section (for Methods and Results) |
|---|---|
| Product Information/Prescribing Information | A |
| Background Information<br>Previous DMEPA HF Reviews | B |

[a] Whaley, E. Human Factors Validation Study Protocol Review for Efanesoctocog alfa for injection (IND 17464). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2022 JAN 19. RCM No.: 2021-2061.

| Table 1. Materials Considered for this Label and Labeling Review | |
|---|---|
| **Material Reviewed** | **Appendix Section (for Methods and Results)** |
| Background Information on Human Factors Engineering (HFE) Process | C |
| Human Factors Validation Study Report | D |
| Information Requests Issued During the Review | E-N/A |
| Instructions for Use (IFU) | F |

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed, and our analysis to determine if the user interface supports the safe and effective use of the proposed product.

### 3.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the HF validation study design. See Appendix C for more details on the study design.

| Table 2. Study Methodology for Human Factors (HF) Validation Study | |
|---|---|
| **Study Design Elements** | **Details** |
| **Participants**[bc] | • Adult males with hemophilia A (n=15)<br>• Adolescent males aged 11 to 18 years with hemophilia A (n=15)<br>• Healthcare professionals (HCPs) (nurses) currently treating patients with hemophilia (n=15) |

[b] The Applicant states that caregivers are intended users of the proposed product; however, the HF validation study did not include a distinct user group of caregiver participants. We generally expect the inclusion of all intended users in the HF validation study. However, we are aware that most patients with hemophilia A are accustomed to administering intravenous therapy. Furthermore, the proposed product is similar to a marketed product, Eloctate, in terms of uses, users, use environments, and the user interface. Therefore, in this instance, the exclusion of caregiver participants does not preclude our review of the HF validation study results.

[c] The HF validation study did not include distinct user groups of injection-naïve and injection-experienced participants. However, HCPs and most patients with hemophilia A are accustomed to intravenous therapy and are likely to have injection experience. Furthermore, the proposed product is similar to a marketed product, Eloctate, in terms of uses, users, use environments, and the user interface. Therefore, in this instance, the exclusion of distinct injection-naïve and injection-experienced participants does not preclude our review of the HF validation study results.

| | |
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| **Training**[d] | • HCP participants were untrained<br>• All patient participants were trained by an HCP:<br>  ○ In a one-on-one session, the trainer gave the participant the IFU and guided him/her through the content of the document. The trainer used a ALTUVIIIO procedural pack, and an infusion set, to demonstrate the procedure step by step and answered any questions the participant had<br>  ○ The trainer asked then the participant to use a ALTUVIIIO procedural pack and an infusion set to perform an infusion into an injection pad. The trainer answered questions and provided guidance as needed for the participant to complete the injection successfully<br>  ○ The trainer assessed whether the participant had successfully been trained and was prepared for subsequent self-injection<br>  ○ Because the treatment frequency for ALTUVIIIO is once weekly, each participant was asked to return 1 day (24 -36 hours) after their training session to take part in their study session, at which they performed the handling and knowledge tasks |
| **Test Environment** | Patients:<br>• resembled a home environment with regard to furnishings (e.g., table, chairs) and lighting level.<br>HCPs:<br>• resembled a clinical environment with regard to room furnishings (e.g., table, chairs) and lighting level. |
| **Test Materials** | • ALTUVIIIO package including (LOT: 12345):<br>  ○ (b) (4) sealed vial with powder/placebo (item code supplier: (b) (4) Yellow)<br>  ○ Vial label 250 IU (LOT:123456)<br>  ○ (b) (4) prefilled diluent syringe (item code Supplier: (b) (4) )<br>  ○ (b) (4) 20mm vial adapter in its package (item code supplier: (b) (4) ) |

[d] The HF validation study included trained patient participants. We generally expect the HF validation study evaluate the user interface in the absence of training in cases where training would be appropriate but is not expected to occur routinely or consistently. However, per the FDA Clinical Reviewer, patients with hemophilia A are routinely provided training. Therefore, in this instance, the absence of untrained patient participants does not preclude our review of the HF validation study results.

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|---|---|
| | ○ (b) (4) plunger rod (item code supplier: (b) (4) )<br>○ Instructions for Use (IFU)<br><br>• Supplies available separately from the proposed product[e]<br>○ Infusion set ((b) (4)® winged infusion set with 25G x ¾ (0.5 x 19 mm))<br>○ Alcohol wipes<br>○ FDA sharps disposal container<br>○ Tape<br>○ Tourniquet<br>○ Bandage<br>○ Gloves (for HCP sessions)<br><br>• Supplies for simulated use scenario:<br>○ Trash can<br>○ Injection pad (for patient sessions)<br>○ Injection pad applied on the manikin (for HCP sessions)<br>○ Hand sanitizer |
| **Sequence of Study** | • Simulated Use Scenario<br>○ Participants will use the proposed product and an infusion kit to deliver an injection into an injection pad.<br>○ This scenario will be followed by debriefing/subjective feedback.<br>• Knowledge Task Questions<br>○ This scenario will be followed by debriefing/subjective feedback. |

## 4 RESULTS AND ANALYSES

Table 3 describes the study results, Applicant's analyses of the results, and DMEPA's analyses and recommendations.

[e] These supplies need to be acquired separately by the user for administration of the proposed product. Some of these supplies (e.g., infusion set, tourniquet, etc.) may be 510(k) cleared medical devices. Given that the intended user population may be familiar with other similar marketed products (e.g., Eloctate) that also require use of these supplies, our review generally focuses on user interface elements that are specific to the proposed product.

**Table 3. Identified Issues and DMEPA's Analysis and Findings**

**Legend:**
**A#: Adult male patients**
**ACG#: Adolescent male patients**
**N#: HCPs**

| | Identified Issue | DMEPA's Analysis and Findings |
|---|---|---|
| 1. | For the task *User checks the expiration date*, see the table and list below for a summary of use-related events.<br><br>Total number of UE, CC, UD: Use errors (n=4)<br>Type of Participants: (b) (6)<br><br>Use-related events include:<br>• (b) (6) mentioned that he was unsure about quality of the reconstituted solution and decided to take a new package. He performed all steps once again and proceeded with the injection. He didn't check the expiration during the second time. *"Since they were right next to each other I did not look at it. When they sit together, are delivered together they are the same expiration date and I assumed they had both the same expiration date."*<br>• (b) (6) did not check the expiration date. *"I forgot to check the date when it expires - I would have checked the box when it expires."*<br>(b) (6)'s caregiver: *"I put the medicine on … he takes it and puts it in."*<br>(b) (6) wasn't able to articulate further why he forgot to check the expiration date. Caregiver mentioned in debrief that at home, she prepares the medicine.<br>• (b) (6) did not check the expiration date. | The subjective feedback indicated study artifact may have contributed to the use error due to the participants awareness of the simulated use nature of the study. Specifically, all four participants who experienced use errors alluded to the premise that in actual use, they expected the expiration date to be checked before receiving the product or expected that the product would be in date prior to dispensing.<br><br>We also note that checking the expiration date is a task common to other marketed biologic products and is not unique to the proposed product.<br><br>Based on our review of the subjective feedback and RCA, we did not identify areas of improvement and have no recommendations at this time. |

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“I would check on the vial. Today I actually did not check it but this is something you should do. At work I think about it but not for this setting.”<br>
• (b) (6) did not check the expiration date.<br>
“Normally patients get it from the in-house pharmacy that already dispenses it correctly.”<br><br>
The Applicant provided the following root cause analysis (RCA):<br>
• Test artifact: Due to the artificial nature of the test situation, participants did assume that there is no need to check the drug conditions.<br><br>
Based on the URRA, if this task is omitted or not performed correctly there is risk of degraded drug (greater than 30% below the target dose) leading to an underdose, which may result in hemorrhage.<br><br>
The Applicant did not propose additional mitigations in response to the use related event for this task.
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<td>2.</td>
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For the task User inserts vial adapter spike into vial stopper, see the table and list below for a summary of use-related events.<br><br>
<table>
<tr><td>Total number of UE, CC, UD</td><td>Type of Participants</td></tr>
<tr><td>Use Errors (n=2)</td><td>(b) (6)</td></tr>
<tr><td>Close calls (n=1)</td><td>(b) (6)</td></tr>
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<br>
Use-related event includes:<br>
• (b) (6) took the adapter out of the cover to put it on the vial and touched the inside.<br>
"I pulled out the adapter [from the cover], based on in which package it is it will just fall out. But I pulled it out which I thought was fine because I was wearing gloves. If I was doing everything safely for the patient, you don't want to
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Our review of the study results did not identify subjective feedback or root cause analysis that indicated the user interface contributed to the use-related event.<br><br>
Our review of the user interface finds that Step 6 of the IFU describes pushing the vial adapter straight down until the spike on the vial adapter punctures the center of the vial stopper and is fully inserted. Additionally, Step 5 of the IFU includes a statement not to remove the vial adapter from the packaging or touch the inside of the vial adapter. The vial adapter is a cleared medical device that is used with other marketed products and inserting the vial adapter into the vial is not unique to the proposed product. Thus, the Applicant has mitigated the residual risk to the extent feasible.
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touch it with your bare hands but with gloves I thought it was safe. And I did it [pulled it out] just to get it out."
<ul>
<li>(b) (6) flipped the vial upside down and pushed the vial onto the adapter instead of the adapter onto the vial standing on the table. (b) (6) was nervous and distracted because of unusual setting.</li>
<li>(b) (6) pressed the vial adapter onto the vial but later when screwing on the syringe he wondered whether it was on correctly because it was slightly askew. Took the syringe off and tried to press it down.<br>"I thought I heard the click, but I think it didn't go on quite right and if I tried putting in the liquid from the syringe into the vial it might leak out because the spike was not breaking through the covering. I tried fixing it [by pressing it down."</li>
</ul>
The Applicant provided the following root cause analysis (RCA):
<ul>
<li>(b) (6) recognized the incorrect vial adapter placement and self-corrected.</li>
<li>(b) (6): The observed incorrect use would not result in compromised medical care.</li>
</ul>
Based on the URRA, if this task is omitted or not performed correctly there is risk of no dose, which may result in hemorrhage.<br><br>
The Applicant did not propose additional mitigations in response to the use related event for this task.
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<td>Based on our review of the user interface, subjective feedback, and RCA, we did not identify areas of improvement and have no recommendations at this time.</td>
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For the task User dissolves powder into solution by swirling, see the table and list below for a summary of use-related events.<br><br>
<table>
<tr><td>Total number of UE, CC, UD</td><td>Type of Participants</td></tr>
<tr><td>Use Errors (n=4)</td><td>(b) (6)</td></tr>
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<br>
Use-related event includes:
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Our review of the study results identified subjective feedback from one participant that indicated the user interface contributed to the use-related event. Specifically, participant (b) (6) states she looked at the graphic in the IFU and determined she should flip the vial over instead of swirling.<br><br>
Our review of the user interface finds that Step 13 of the IFU describes gently swirling the vial until the powder is completely
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| | • (b) (6) didn't swirl the solution. He just turned the vial and pulled the solution back to the syringe.<br>*"I did not swirl, I normally don't. It reconstitutes fast enough with the turbulence from putting the water into it, it dissolves the product in seconds. And when I observed it there were no particles in it so it didn't need it. And the time given I needed to prepare the next step it had enough time to dissolve without my involvement."*<br>• (b) (6) shook the vial instead of gently swirling.<br>*"You got to shake to mix the actual medication with the saline. Usually with a powdered medication that you are reconstituting I shake it until I saw no more powdery particles."*<br>• (b) (6) did not swirl and only moved it for a short time.<br>*"If you push the saline in and then turn the vial to draw it back it will mix. You can shake a little bit, but the powder is very easily dissolved. It automatically dissolves but you can turn it upside down a few times. But you have to make sure there are no crystals, and it is clear."*<br>She did not use/read the IFU.<br>• (b) (6) performed all steps two times. First time she didn't fully understand the study task and just simulated the actions and didn't perform tasks as she would do that in real life. She was asked to perform all steps once again. First time: (b) (6) did not swirl but shook the vial. Second time: (b) (6) did not shake the vial, only turned it upside down as soon as the solution was in and directly drew it up in the syringe again.<br>*"I am not shaking it 'do not shake'." I did what the instructions said and just flipped it over." MOD did you read this in instruction, (b) (6): "Yes I looked at the picture."*<br><br>The Applicant provided the following root cause analysis (RCA):<br>• (b) (6): Negative transfer | dissolved. Step 13 also includes the statement, "Do not shake" and arrows which illustrate a swirling action. Dissolving the powder in the diluent is common to other injectable products provided as a powder and is not unique to the proposed product.<br><br>Based on our review of the user interface, subjective feedback, and RCA, we did not identify areas of improvement and have no recommendations at this time. |

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<ul>
<li>(b) (6): Test artifact</li>
<li>(b) (6): RCA not provided</li>
</ul>
<br>
Based on the URRA, if this task is omitted or not performed correctly there is risk of underdose due to reduced volume greater than 30% below the target dose, which may result in hemorrhage.<br><br>
The Applicant did not propose additional mitigations in response to the use related event for this task.
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<td>4.</td>
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For the task User removes reconstitution syringe from vial adapter, see the table and list below for a summary of use-related events.<br><br>
<table>
<tr><td>Total number of UE, CC, UD</td><td>Type of Participants</td></tr>
<tr><td>Close Calls (n=1)</td><td>(b) (6)</td></tr>
<tr><td>Use Difficulties (n=1)</td><td>(b) (6)</td></tr>
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Use-related event includes:
<ul>
<li>(b) (6) did not transfer the mixed medicine back into a syringe, first turned the syringe in a wrong direction and overtightened it, the rigid part of the syringe cap came off, so she was not able to transfer the mixed medicine back to the syringe. After looking at IFU she noticed the mistake, stated she would start over with a new one and received a new package from the MOD.<br>
During task, after looking at IFU (b) (6): “So I wasn’t supposed to pull the plunger off the vial until it was fully mixed and back into the syringe.”<br>
MOD what would you do at work: “I would grab another medication, a completely new package. You’re not supposed to mess with this kind of medicine it is very sensitive.”<br>
During follow up: “I assumed that there was going to be some other sort of connective device that I would have to</li>
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Although one participant experienced a close call and one participant experienced a use difficulty, both participants completed the task.<br><br>
Our review of the study results did not identify subjective feedback or root cause analysis that indicated the user interface contributed to the use-related event.<br><br>
Our review of the user interface finds that Step 15 of the IFU describes removing the diluent syringe from the vial adapter by turning it clockwise. Both the vial adapter and diluent syringe are cleared medical devices. Furthermore, removing the diluent syringe from the vial adapter is common to other injectable products that are available as a powder and require reconstitution from a diluent syringe and is not unique to the proposed product.<br><br>
Based on our review of the user interface, subjective feedback, and RCA, we did not identify areas of improvement and have no recommendations at this time.
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<td>attach onto it. I didn’t know the medicine would go directly through the adapter. I detached the syringe because I thought there would be another part I had to attach to the syringe. The second time I realized there was the tiny spike in the vial where the medication would go through. The first time the white piece just came off by accident, but I think I forced it off. The second time I was more careful.”<br>• (b) (6) first turned the vial in the wrong direction but figured it out and unscrewed it successfully.<br><br>The Applicant provided the following root cause analysis (RCA):<br>• (b) (6): The observed difficulty would not result in compromised medical care.<br>• (b) (6): Negative transfer<br><br>Based on the URRA, if this task is omitted or not performed correctly there is risk of delay of therapy.<br><br>The Applicant did not propose additional mitigations in response to the use related event for this task.</td>
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<td>5.</td>
<td>For the task User attaches the syringe to the infusion set connector, see the table and list below for a summary of use-related events.<br><br>
<table>
<tr><td>Total number of UE, CC, UD</td><td>Type of Participants</td></tr>
<tr><td>Close Calls (n=1)</td><td>(b) (6)</td></tr>
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<br>Use-related event includes:<br>• (b) (6) after mixing, disconnected the syringe from the vial, turned the syringe in a wrong direction and overtightened it, the rigid part of the syringe cap came off. (b) (6) was struggling to connect the syringe with the infusion set connector, but finally connected the syringe with the infusion set (without rigid part) and performed the injection successfully.</td>
<td>Although the participant experienced a close call, she was able to complete the task.<br><br>Our review of the study results did not identify subjective feedback or root cause analysis that indicated the user interface contributed to the use-related event.<br><br>Our review of the user interface finds that Step 16 of the IFU describes attaching the syringe to the infusion set connector. Furthermore, the syringe is a cleared medical device that is used with other marketed products and attaching the syringe to the infusion set connector is common to other marketed products that require delivery through an infusion set and is not unique to the</td>
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<td>"It says gently unscrew so maybe I was too tough with it so that it stayed on. Maybe if I had done it more gently with the correct turn of the vial adapter this would have stayed where it is supposed to be, It doesn't seem like you have to hold it with your fingers according to IFU."<br><br>The Applicant provided the following root cause analysis (RCA):<br>• (b) (6) was able to inject the full dose even though the luer lock connector on the syringe was missing.<br><br>Based on the URRA, if this task is omitted or not performed correctly there is risk of no dose or underdose due to reduced volume greater than 30% below the target dose, which may result in hemorrhage.<br><br>The Applicant did not propose additional mitigations in response to the use related event for this task.</td>
<td>proposed product. Thus, the Applicant has mitigated the residual risk to the extent feasible.<br><br>Based on our review of the user interface, subjective feedback, and RCA, we did not identify areas of improvement and have no recommendations at this time.</td>
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<td>6.</td>
<td>For the task User applies tourniquet, see the table and list below for a summary of use-related events.<br><br>
<table>
<tr><td>Total number of UE, CC, UD</td><td>Type of Participants</td></tr>
<tr><td>Use Errors (n=2)</td><td>(b) (6)</td></tr>
<tr><td>Close Calls (n=1)</td><td>(b) (6)</td></tr>
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<br>Use-related event includes:<br>• (b) (6) didn’t apply tourniquet. Did it after the needle was already inserted after looking at IFU and realizing he had not applied it.<br>“I wouldn’t have been able to find a vein without the tourniquet. I just missed it. I think because of routine, you do the steps a hundred times, and you think you know it all, just do it from memory. With the fake arm on, you think you are ready because the veins are popping out.”<br>• (b) (6) didn’t apply the tourniquet.</td>
<td>The subjective feedback indicated study artifact contributed to the use error. Specifically, the use of a fake arm influenced the participants behavior not to apply a tourniquet.<br><br>Based on our review of the subjective feedback and RCA, we did not identify areas of improvement and have no recommendations at this time.</td>
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“Normally I would put the tourniquet on but because I was seeing the vein (on the fake arm) I wasn’t thinking about it. Normally I wouldn’t be able to see the vein and would put the tourniquet on.”
<ul>
<li>(b) (6) didn’t apply the tourniquet and recognized that before he inserted the needle into a “vein”. He put the syringe with the needle attached on the table, applied the tourniquet, connected the new needle to the syringe luer lock connector, primed the needle and the tubing, cleaned the injection site again, and finally inserted the needle.<br>“I messed that up. Can I have another needle please?”</li>
</ul>
The Applicant provided the following root cause analysis (RCA):
<ul>
<li>(b) (6) : Test artifact</li>
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Based on the URRA, if this task is omitted or not performed correctly there is risk of no dose, which may result in hemorrhage.<br><br>
The Applicant did not propose additional mitigations in response to the use related event for this task.
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<td>7.</td>
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For the task User removes air from the syringe, see the table and list below for a summary of use-related events.
<table>
<tr><td>Total number of UE, CC, UD</td><td>Type of Participants</td></tr>
<tr><td>Use Errors (n=4)</td><td>(b) (6)</td></tr>
<tr><td>Close Calls (n=3)</td><td>(b) (6)</td></tr>
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Use-related event includes:
<ul>
<li>(b) (6) did not remove the air from the tubing.<br>“I didn’t do it because I did not see any air bubbles. If I see one, I push it out. I was taught to do it like this years ago.”</li>
<li>(b) (6) did not remove the air. (b) (6) confirmed during debrief that he would prime at home. (b) (6) was extremely</li>
</ul>
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<td>
Our review of the study results did not identify subjective feedback or root cause analysis that indicated the user interface contributed to the use-related event.<br><br>
Our review of the user interface finds that Step 18 of the IFU describes removing air from the syringe similar to other similar marketed products for the same intended users. We note the infusion set is a cleared medical device not provided with the proposed product and users must acquire the infusion set separately. Additionally, removing air from the syringe prior to infusing is a common task for products that are administered by intravenous infusion and is not unique to the proposed product. Thus, the Applicant has mitigated the residual risk to the extent feasible.
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| | nervous during process. Caregiver mentioned in the debrief that at home, she would tell/interrupt him when she noticed that he forgot to prime.<br>• (b) (6) performed all steps two times. First time she didn't fully understand the study task and just simulated the actions and didn't perform tasks as she would do in real life. First time she primed, second time she did not prime it.<br>*"Normally I would have a saline flush, prime it with saline. At my practice we do not have a tubing, just a little port. I didn't prime it today. I think because of the nature of this setting, I didn't have the saline here, so I didn't think about it. I focused on the new drug, but I would have a saline flush first. I think what threw me off was that it came with a tubing and not a port. I would flush it with saline and not the drug to not waste medication. At this point I was thinking about losing medication. After realizing what IFU said: I guess I just missed it, I was distracted with the adapter and the extra supplies. And in real life the needle wouldn't be connected to the patient arm already. The habit is I flush my tubing first to make sure it is in the vein."*<br>• Participant (b) (6) didn't connect the syringe to the infusion set and removed the air from the syringe by pushing the plunger rod. Then inserted the needle and then connected to the syringe.<br>*"Some people prime it. The downside with priming is when you prime it and you insert the needle in the vein you cannot see the blood because the factor is blocking the needle and patients keep pocking even though they are already in the vein." MOD prompt how can be sure this was correct approach for this medication (b) (6): "I consider this for the in-clinic infusion. For patients for self-infusion, I give them the two options, priming the needle or doing it this way, depending on what they prefer."*<br>• (b) (6) didn't remove the air from the syringe and tubing, | Based on our review of the user interface, subjective feedback, and RCA, we did not identify areas of improvement and have no recommendations at this time. However, we defer to CBER to determine whether the residual risk is acceptable given the potential for air embolism, no dose or underdose, which may result in hemorrhage. |

| | | |
|---|---|---|
| | inserted the needle into a "vein," recognized it immediately and asked for another syringe.<br>*"I had put the needle into my arm, forgetting to prime it. Hence why I took it out and had to read it all. At home I would have used the same needle but at hospitals they use different needles even for just one injection." MOD prompt why happened, (b) (6): "Maybe it was habit. I forget a lot of things. Usually, my mother is there and would warn me before I did anything wrong. Or reading the IFU but I felt like reading the IFU one day before I could just skim through it today."*<br>• (b) (6) didn't remove the air from the syringe and tubing, inserted the needle into a "vein," recognized it immediately and asked for another syringe.<br>*"I took the needle cover off, but I had to prime it first and then that like caught my attention and then I got a new one [needle] and then primed it and then took the cover off. I forgot because I think I maybe skipped a step in the IFU."*<br>• (b) (6) pushed plunger rod too far and lost some diluent. She realized her mistake immediately.<br>*"I tried to push gently but it was a little harder than I expected. And the tube is very narrow, and it is difficult to see where the solution/air is and how much I have to remove. There could be more detail about removing the air or preparing the tube and how much air to remove. The solution was very clear, and I didn't see it going up."*<br><br>The Applicant provided the following root cause analysis (RCA):<br>• (b) (6): Negative transfer<br>• (b) (6): Test artifact<br>• (b) (6): stated that he would not perform this task step unsupervised in real life.<br>• (b) (6): skipped the task first but then recognized the failure and self-corrected. | |

<table>
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<td>
<ul>
<li>(b) (6): recognized the diluent spread out and stopped pushing the plunger, self-corrected. The remaining amount of diluent constituted the full dose.</li>
</ul>
Based on the URRA, if this task is omitted or not performed correctly there is risk of air injected into vein, which may result in air embolism or there is risk of no dose or underdose, which may result in hemorrhage.
The Applicant did not propose additional mitigations in response to the use related event for this task.
</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>
For the task User removes the needle, see the table and list below for a summary of use-related events.
<table>
<tr><td>Total number of UE, CC, UD</td><td>Type of Participants</td></tr>
<tr><td>Use Errors (n=1)</td><td>(b) (6)</td></tr>
</table>
Use-related event includes:
<ul>
<li>(b) (6) performed all steps two times. First time she didn’t fully understand the study task and just simulated the actions and didn’t performed tasks as she would do that in real life. (b) (6) didn’t inject the entire dose and remove the needle. First time (b) (6) did not press down the plunger; Second time pressed it down half the way then stopped. (b) (6) during second time: “I just don’t know. It’s a mannequin. Am I supposed to infuse everything?”<br>Follow up (b) (6): “I didn’t administer the full dose because it is a mannequin and with the mannequins at my work they don’t want us to put fluid in there.”</li>
</ul>
The Applicant provided the following root cause analysis (RCA):
<ul>
<li>Test artifact/negative transfer</li>
</ul>
</td>
<td>
Our review of the subjective feedback indicated the participant did not remove the needle due to study artifact. Specifically, the participant did not think all tasks needed to be completed because she was using a mannequin.
Based on our review of the subjective feedback and RCA, we have no recommendations at this time.
</td>
</tr>
</table>

<table>
<tr><td></td><td>Based on the URRA, if this task is omitted or not performed correctly there is risk of underdose, which may result in hemorrhage.<br><br>The Applicant did not propose additional mitigations in response to the use related event for this task.</td><td></td></tr>
<tr><td colspan="3">Knowledge Assessment Tasks</td></tr>
<tr><td>9.</td><td>For the knowledge assessment task How should you store the ALTUVIIIO before you use it? see the table and list below for a summary of use-related events.<br><br><table><tr><td>Total number of UE, CC, UD</td><td>Type of Participants</td></tr><tr><td>Use Errors (n=1)</td><td>(b) (6)</td></tr></table><br>Use-related event includes:<ul><li>(b) (6) did not mention “In the refrigerator between 36°F and 46°F” and mentioned “at room temperature.” She did not read the IFU and answered based on her experiences with other products.</li></ul>The Applicant provided the following root cause analysis (RCA):<ul><li>Since (b) (6) did not refer to the relevant steps in the IFU during IFU assessment task, she was not aware of the instructions provided in the IFU. (b) (6) refused to use the IFU.</li></ul>Based on the URRA, if this task is omitted or not performed correctly there is risk of underdose due to degraded drug greater than 30% below the target dose, which may result in hemorrhage.<br><br>The Applicant did not propose additional mitigations in response to the use related event for this task.</td><td>Our review of the study results did not identify subjective feedback or root cause analysis that indicated the user interface contributed to the use-related event.<br><br>Based on our review of the subjective feedback and RCA, we have no recommendations at this time.</td></tr>
</table>

<table>
<tr>
<td>10.</td>
<td>For the knowledge assessment task What do the instructions say about what you should not do while letting the ALTUVIIIO come up to room temperature? see the table and list below for a summary of use-related events.<br><br>
<table>
<tr><td>Total number of UE, CC, UD</td><td>Type of Participants</td></tr>
<tr><td>Use Errors (n=2)</td><td>(b) (6)</td></tr>
</table>
<br>Use-related event includes:<br>
• (b) (6) didn’t mention exactly the wording “Do not put in direct sunlight” but said: “avoid all kinds of external heat sources.” Did not read the IFU and tried to answer based on memory.<br>
• (b) (6) didn't mention external heat sources. (b) (6) found the correct section in the IFU as he was able to mention “to avoid sunlight, not to use it in hot water and to not freeze it.”<br><br>
The Applicant provided the following root cause analysis (RCA):<br>
• (b) (6): Since this participant did not refer to the relevant steps in the IFU during IFU assessment task, he was not aware of the exact wording in the IFU<br>
• Participant (b) (6) found the section containing this information but didn’t verbalize the entire section. (b) (6) is aware of the risks related to the incorrect warm up.<br><br>
Based on the URRA, if this task is omitted or not performed correctly there is risk of underdose due to degraded drug greater than 30% below the target dose, which may result in hemorrhage.<br><br>
The Applicant did not propose additional mitigations in response to the use related event for this task.</td>
<td>Our review of the study results did not identify subjective feedback or root cause analysis that indicated the user interface contributed to the use-related event.<br><br>
Based on our review, we find the IFU includes the statement, “Do not use external heat sources such as putting the vial or prefilled diluent syringe in hot water.” in the storage section. However, this bullet does not immediately follow the bullet, “Remove the product kit from the refrigerator and allow the ALTUVIIIO vial and the prefilled diluent syringe to come to room temperature prior to injection.” Therefore, the related information about external heat sources may be overlooked by users. Although there was no subjective feedback which pointed to confusion or deficiencies related to the storage information in the IFU, we find the IFU can be improved to group related storage statements close together. Thus, we provide a recommendation in the Identified Issues and Recommendation Table for the Applicant to revise the IFU so that the statement regarding external heat sources immediately follows the statement regarding allowing the syringe to come to room temperature. We determined that this revision can be implemented without submission of additional HF validation testing data for review.</td>
</tr>
<tr>
<td>11.</td>
<td>For the knowledge assessment task What should you look for when you get your kit from refrigerator? see the table and list below for a summary of use-related events.</td>
<td>Our review of the study results did not identify subjective feedback or root cause analysis that indicated the user interface contributed to the use-related event.</td>
</tr>
</table>

| Total number of UE, CC, UD | Type of Participants |
|---|---|
| Use Errors (n=10) | (b) (6) |

Use-related event includes:

- (b) (6) didn't mention "dose": *"The expiration date… and to make sure that it's the correct medicine"*
- (b) (6) didn't mention "medicine": *"Check that you have the correct dose and the expiration date"*
- (b) (6) didn't mention "medicine": *"You look for...that it's the correct dosage, whatever your dosage is, and that it's not expired"*
- (b) (6) didn't mention "medicine" *"Making sure the amount is right... the amount that you're taking".*
- (b) (6) didn't mention "medicine": *"Any damage or the expiration date [...] Dosage as well"*
- (b) (6) didn't mention "medication": "*The expiration date and that it's the right dose."*
- (b) (6) didn't mention "medication": "*The strength of the unit."*
- (b) (6) didn't mention "medication": *"That it's the correct dose… and it's not expired."*
- (b) (6) didn't provide the complete answer, didn't mention "dose": *"If I was at work and pulling this for a patient, then I would make sure it's their medication […] so you know that this specific package and everything is for the patient".*
- (b) (6) didn't provide the complete answer, didn't mention "medication": "*You know when you're going to get the dose"*

The Applicant provided the following root cause analysis (RCA):

Our review of the user interface finds that Step 1 of the IFU describes checking for the correct medicine and dose. Checking the medication and dose is common to other marketed products and is not unique to the proposed product.

Based on our review of the user interface, subjective feedback, and RCA, we did not identify areas of improvement and have no recommendations at this time.

<table>
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<ul><li>The words “medicine” and “dose” were used interchangeably. If participants mentioned one of these words, they assumed that they had provided the complete answer to the question.</li></ul>
Based on the URRA, if this task is omitted or not performed correctly there is risk of no dose, which may result in hemorrhage.<br><br>
The Applicant did not propose additional mitigations in response to the use related event for this task.
</td><td></td></tr>
<tr><td>12.</td><td>
For the knowledge assessment task What should you do if you need more than one vial for your dosage? see the table and list below for a summary of use-related events.<br><br>
<table>
<tr><td>Total number of UE, CC, UD</td><td>Type of Participants</td></tr>
<tr><td>Use Errors (n=1)</td><td>(b) (6)</td></tr>
</table>
<br>
Use-related event includes:
<ul><li>(b) (6) answered from experience about the process of being delivered the wrong dosage for a patient, how she would contact the pharmacy about the dosage. Tried but failed to find the respective section in the IFU.<br>"If I'm a nurse and I know the patient needs more than one vial? So usually the pharmacy will send the exact dose but if I happen to see that it's missing or something, then, at my job we can send a message to pharmacy, for them to send another one. If it's a time sensitive medication then I can call pharmacy and say 'Hey, I only got one vial but maybe I need two'. I mean it says if you have any further questions you can ask your healthcare provider or call this number... so maybe if you realize you don't have any more medication for your big dose you can do that"…"I don't see it".</li></ul>
The Applicant provided the following root cause analysis (RCA):
</td><td>
Our review of the subjective feedback and RCA indicate that study artifact contributed to this use-related event.<br><br>
Based on our review of the subjective feedback and RCA, we have no recommendations at this time.
</td></tr>
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<table>
<tr><td></td><td>

- (b) (6) misunderstood the question as having to deal with being delivered less medication than needed. The explanation provided by N7 and her proposed course of action would not result in harm

Based on the URRA, if this task is omitted or not performed correctly there is risk of underdose, which may result in hemorrhage.

The Applicant did not propose additional mitigations in response to the use related event for this task.
</td><td></td></tr>
<tr><td>13.</td><td>

For the knowledge assessment task *What should you be careful NOT to do while drawing the solution up into the syringe?* see the table and list below for a summary of use-related events.

<table>
<tr><td>Total number of UE, CC, UD</td><td>Type of Participants</td></tr>
<tr><td>Use Errors (n=1)</td><td>(b) (6)</td></tr>
</table>

Use-related event includes:

- (b) (6) didn't find the information in the IFU. She answered to pull it up slowly because you could inadvertently dis-connect syringe and vial

The Applicant provided the following root cause analysis (RCA):

- (b) (6) demonstrated that she was aware of the risks related to pulling out the plunger rod as she performed the task step correctly during the handling task.

Based on the URRA, if this task is omitted or not performed correctly there is risk of no dose, which may result in hemorrhage.

The Applicant did not propose additional mitigations in response to the use related event for this task.
</td><td>

Our review of the study results did not identify subjective feedback or root cause analysis that indicated the user interface contributed to the use-related event.

Our review of the user interface finds that Step 14 of the IFU describes being careful not to pull out the plunger rod. Drawing solution into a syringe without pulling out the plunger rod is common to other marketed products for intravenous infusion and is not unique to the proposed product. Additionally, none of the participants pulled out the plunger rod during the simulated use scenario.

Based on our review of the subjective feedback, and RCA, we find did not identify areas of improvement and have no recommendations at this time.
</td></tr>
<tr><td>14.</td><td>For the knowledge assessment task *How can you know which*</td><td>Although one participant did not give the answer to match the success criteria, the participant did reply that the IFU will contain</td></tr>
</table>

| | | |
|---|---|---|
| | *kind of infusion set you can use with the product?* see the table and list below for a summary of use-related events.<br><br>Total number of UE, CC, UD: Use Errors (n=1); Type of Participants: (b) (6)<br><br>Use-related event includes:<br>• (b) (6) didn't provide the complete answer, didn't mention "Ask your healthcare provider"<br>*"It's included in this here [points to IFU]… they could read the box itself, usually that will list what you need [...] It could be a number of things… A lot of my patients – they get their medicine directly delivered from bleeding disorder pharmacies, so it'll tell you in the little kit that they get."*<br><br>The Applicant provided the following root cause analysis (RCA):<br>• Since this participant did not use/read the relevant steps in the IFU during IFU assessment task, she might not have been aware of the instructions provided in the IFU. She refused to use the IFU.<br><br>Based on the URRA, if this task is omitted or not performed correctly there is risk of underdose, which may result in hemorrhage.<br><br>The Applicant did not propose additional mitigations in response to the use related event for this task. | the information needed to inform the user what infusion set is compatible. We note the participant did not actually read the IFU but pointed to it as a reference document.<br><br>Our review of the study results did not identify subjective feedback or root cause analysis that indicated the user interface contributed to the use-related event.<br><br>Based on our review of the subjective feedback and RCA, we have no recommendations at this time. |

## 4.1 ANALYSIS OF NON-CRITICAL AND CRITICAL TASK ERRORS

The HF validation study showed use errors and use difficulties with the non-critical and critical tasks listed below. Our review of the use errors for the identified critical tasks did not find them to be unique or specific to the proposed combination product and as such are not the focus of this review. Based on our post-market experience with similar products and our review of the available participants' subjective feedback, the Applicant's root cause analysis, and Applicant's proposed risk mitigation strategy, we determined the residual risk for these tasks is acceptable. Subsequently, we did not identify further need for risk mitigation strategies at this time to address the use errors related to the following critical and non-critical tasks:

- User opens the package and removes the components from the packaging
- User removes plastic cap from vial
- User removes the backing from the vial adapter
- User screws the plunger rod into the diluent syringe (critical)
- User removes the tourniquet
- User injects solution by pressing the plunger rod on the syringe (critical)

## 4.2 LABELS AND LABELING

Table 4 below includes the identified medication error issues with the submitted prescribing information (PI) and IFU, our rationale for concern, and our proposed recommendations to minimize the risk for medication error. We recommend CBER consider conveying our recommendations to the applicant prior to taking action on this application.

| **Table 4. Identified PI Issues and Recommendations Bioverativ Therapeutics Inc.** | | | |
|---|---|---|---|
| | **IDENTIFIED ISSUE** | **RATIONALE FOR CONCERN** | **RECOMMENDATION** |
| **Full Prescribing Information – Section 2 Dosage and Administration** | | | |
| 1. | (b) (4) | | |
| **Identified IFU Issues and Recommendations** | | | |
| | **IDENTIFIED ISSUE** | **RATIONALE FOR CONCERN** | **RECOMMENDATION** |

| | | | |
|---|---|---|---|
| 1. | Results from the HF validation study reported use errors with the knowledge task question *What do the instructions say about what you should not do while letting the ALTUVIIIO come up to room temperature?* | Based on the use-related risk analysis (URRA), if this task is omitted or not performed correctly there is risk of underdose due to degraded drug greater than 30% below the target dose, which may result in hemorrhage.<br><br>We acknowledge the IFU provides information not to expose the product to external hear sources; however, we find that the location of this information can be improved. | We recommend relocating the statement, "**Do not** use external heat sources such as putting the vial or prefilled diluent syringe in hot water." Immediately after the statement, "Remove the product kit from the refrigerator and allow the ALTUVIIIO vial and the prefilled diluent syringe to come to room temperature prior to injection." |
| 2. | Step 13 includes instructions for pooling reconstituted vials for combining doses that require more than one vial and refers to the "diluent syringe." However, the term "prefilled diluent syringe" is used in the previous steps. | Inconsistent terminology may result in confusion. | We recommend revising "diluent syringe" to "prefilled diluent syringe" in Step 13 for consistency. |
| 3. | Steps 14, 15, 18, 21, and the "Throwing ALTUVIIIO away" section refer to the "(b) (4)," however, at this point in the use sequence the vial has already been reconstituted with diluent. (b) (4) | Incorrect terminology may result in confusion. | We recommend revising "(b) (4)" to "syringe" in Steps 14, 15, 18, 21, and the "Throwing your ALTUVIIIO away" section. |

## 5 CONCLUSION AND RECOMMENDATIONS FOR CBER

We have completed our review of the human factors (HF) validation study results for ALTUVIIIO ([Antihemophilic Factor (Recombinant), Fc-Von Willebrand Factor-XTEN Fusion Protein]) lyophilized powder for solution for intravenous injection. In response to the specific CBER consult questions, we find:

1. **CBER Question #1: Assess whether the human factors engineering studies adequately evaluate user interactions with the product user interface**

   DMEPA response: The human factors validation study adequately evaluated user interactions with the product user interface.

2. **CBER Question #2: Identify critical tasks that may result in serious harm to the patient or user**

   DMEPA response: All critical tasks that may result in harm (including serious harm)[f] to the patient or user are identified and evaluated in the HF study.

3. **CBER Question #3: Evaluate the effectiveness of risk control measures**

   DMEPA response: We find the risk control measures are generally effective; however, we have recommendations for the labeling (Instructions for Use and Prescribing Information) to address certain use errors, use difficulties, or close calls observed with critical tasks in the HF study. Table 3 provides our detailed analysis of the HF Study results. Table 4 provides our recommendation for the Labels and Labeling that we recommend CBER implement to address areas of vulnerability that may lead to medication errors. Additionally, our discussion on the residual risk of air embolism is provided below for CBER's further consideration.

**Additional discussion regarding residual risk of air embolism**

Several use errors (n=4) and close calls (n=3) occurred with the critical task "**User removes air from the syringe**" prior to inserting the needle into the vein. According to the Applicant, if this task is omitted or not performed correctly, there is risk of air injected into a vein, which may result in air embolism or there is risk of no dose or underdose, which may result in hemorrhage.

[f] Critical tasks are user tasks that, if performed incorrectly or not performed at all, would or could cause harm to the patient or user, where harm is defined to include compromised medical care. See Draft Guidance for Industry: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development (February 2016).

For these errors, we reviewed the Applicant's root cause analysis, participants' subjective feedback, and user interface, including the IFU. Based upon our review, it does not appear that the user interface contributed to the use errors and close calls.

Step 18 of the ALTUVIIIO IFU describes removing air from the syringe using language and graphics similar to other products marketed for the same intended uses by the same intended users. The relevant air removal step of the ALTUVIIIO IFU is shown in Figure 3 below, as compared to the air removal step for the currently marketed product, ELOCTATE, shown in Figure 4.

**Figure 3. Proposed ALTUVIIIO air removal step**

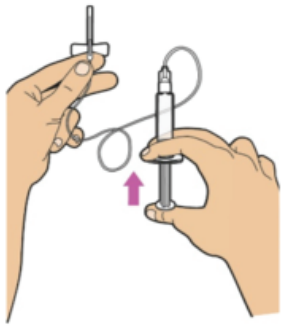
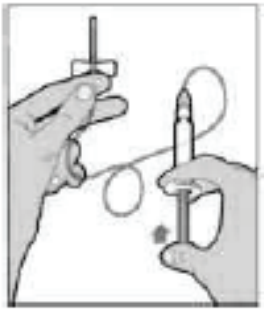
| **Step 18:** | |
|---|---|
|  | Prime the syringe and the tubing. Push the plunger rod until all air is removed from the (b) (4) syringe and ALTUVIIIO has filled the infusion set needle.<br>⚠ **Do not** push ALTUVIIIO through the needle. |

**Figure 4. Marketed ELOCTATE air removal step**

**Step 3**
Depress the plunger until all air is removed from the syringe and ELOCTATE has reached the end of the infusion set tubing.

***Do not** push ELOCTATE through the needle.*



Based on our review of the HF study results report, and the labeling for proposed product and other similar products, we have no specific recommendations to address the risk of air embolism at this time. Thus, we recommend CBER take into consideration the residual risk of air embolism as part of the benefit – risk evaluation for this proposed product.

## 5.1 RECOMMENDATIONS FOR CBER

Provided CBER finds the residual risk of air embolism acceptable, we find the human factors (HF) validation study adequate to support the proposed ALTUVIIIO intravenous infusion product. We recommend CBER implement our recommendations provided in Table 4 to address areas of vulnerability that may lead to medication errors.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

## APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for ALTUVIIIO that Bioverativ Therapeutics Inc. submitted on June 30, 2022.

**Table 5. Relevant Product Information for ALTUVIIIO**

| | |
|---|---|
| **Initial Approval Date** | N/A |
| **Active Ingredient** | Antihemophilic Factor (Recombinant), Fc-Von Willebrand Factor-XTEN Fusion Protein |
| **Indication** | ALTUVIIIO is a long-acting recombinant antihemophilic factor (coagulation factor VIII) with high sustained FVIII activity indicated in adults and children with hemophilia A (congenital factor VIII deficiency) for:<br>• Routine prophylaxis to reduce the frequency of bleeding episodes,<br>• On demand treatment & control of bleeding episodes,<br>• Perioperative management of bleeding |
| **Route of Administration** | intravenous |
| **Dosage Form** | lyophilized powder for solution |
| **Strength** | 250 units, 500 units, 750 units, 1,000 units, 2,000 units, 3,000 units, or 4,000 units |
| **Dose and Frequency** | • Routine prophylaxis:<br>50 units/kg once weekly<br>• On-demand Treatment and Control of Bleeding Episodes: |

| Type of Bleeding | Recommended Dose | Additional Information |
|---|---|---|
| **Minor and Moderate**<br>For example: uncomplicated joint bleeds, minor muscular bleeds, mucosal or subcutaneous bleeds | Single dose of 50 IU/kg | For minor and moderate bleeding episodes occurring within 2 to 3 days after a prophylactic dose, a lower dose of 30 IU/kg dose may be used.<br>Additional doses of 30 or 50 IU/kg every 2 to 3 days may be considered. |
| **Major**<br>For example: Intracranial, retroperitoneal, iliopsoas and neck bleeds, muscle bleeds with compartment syndrome and bleeds associated with a significant decrease in the hemoglobin level | Single dose of 50 IU/kg | Additional doses of 30 or 50 IU/kg every 2 to 3 days can be considered. |

• Perioperative Management:

| Type of Surgery | Pre-operative Dose | Post-operative Dose |
|---|---|---|
| **Minor** | Single dose of 50 IU/kg | An additional dose of 30 or 50 IU/kg after 2 to 3 days may be considered. |
| **Major**<br>For example: Intracranial, intra-abdominal, joint replacement surgery, or complicated dental procedures. | Single dose of 50 IU/kg | Additional doses of 30 or 50 IU/kg every 2 to 3 days may be administered as clinically needed for perioperative management. |

| | |
|---|---|
| **How Supplied** | ALTUVIIIO is supplied in kits comprising a single-dose vial containing lyophilized efanesoctocog alfa powder and device constituent parts that include a prefilled syringe (PFS) containing 3 mL sterile water diluent, plunger rod, and vial adapter. |
| **Storage** | • Store ALTUVIIIO in the original package to protect the ALTUVIIIO vials from light.<br>• Store ALTUVIIIO in powder form at 2°C to 8°C (36°F to 46°F). Do not freeze to avoid damage to the pre-filled diluent syringe.<br>• ALTUVIIIO may be stored at room temperature, not to exceed 30°C (86°F), for a single period of up to 6 months, within the expiration date printed on the label.<br>• If stored at room temperature, record the date that ALTUVIIIO is removed from refrigeration on the carton in the area provided. After storage at room temperature, do not return the product to the refrigerator.<br>• Do not use beyond the expiration date printed on the vial or 6 months after the date that was written on the carton, whichever is earlier.<br>After Reconstitution:<br>• The reconstituted product may be stored at room temperature, not to exceed 30°C (86°F), for up to 3 hours. Protect from direct sunlight. After reconstitution, if the product is not used within 3 hours, it must be discarded. |
| **Container Closure/Device Constituent** | prefilled syringe (PFS) containing 3 mL sterile water diluent, plunger rod, and vial adapter |
| **Intended Users** | Patients (adults and adolescents)<br>Caregivers<br>HCPs |
| **Intended Use Environment** | Home<br>Clinic |

## APPENDIX B. PREVIOUS HF REVIEWS

### B.1.1 Methods

On September 30, 2022, we searched for previous DMEPA reviews relevant to this current review using the term, efanesoctocog alfa.

### B.1.2 Results

Our search identified one previous review[g] and we confirmed that our previous recommendations were implemented or considered.

## APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in the HF results report. See Appendix D.

## APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report:

hfe-summary-report-biv0001.pdf

## APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW-N/A

Not applicable.

## APPENDIX F. INSTRUCTIONS FOR USE (IFU)

### F.1 Instructions for Use (IFU) Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[h] along with our postmarket medication error experience with similar products, we reviewed the ALTUVIIIO Instructions for Use (IFU) submitted by Bioverativ Therapeutics Inc.

- Instructions for Use received on June 30, 2022

proposedifu.docx

[g] Whaley, E. Human Factors Validation Study Protocol Review for Efanesoctocog alfa for injection (IND 17464). Silver Spring (MD): FDA, CDER, OSE, DMEPA2 (US); 2022 JAN 19. RCM No.: 2021-2061.

[h] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.